AR201-13651A

HIGH PRODUCTION VOLUME (HPV) CHEMICAL CHALLENGE PROGRAM

TEST PLAN

for

FATTY ACID DIMERS AND TRIMER

CAS No. 61788-89-4
CAS No. 68937-90-6
CAS No. 68783-41-5
CAS No. 71808-39-4

Submitted to the US EPA

By

The Pine Chemicals Association, Inc.
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HPV Task Force
Consortium Registration #

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Test Plan for Fatty Acid Dimers and Trimer

Summary

The Pine Chemicals Association, Inc. (PCA) is sponsoring 36 HPV chemicals. This Test Plan addresses the following four substances, known collectively as Fatty Acid Dimers and Trimer:

CAS Number	IUR Name	Common Name
61788-89-4	Fatty acids, C18-unsaturated, dimers	Dimer
68937-90-6	Fatty acids, C18-unsaturated, trimers	Trimer
68783-41-5	Fatty acids, C18-unsaturated, dimers, hydrogenated	Hydrogenated dimer
71808-39-4	Fatty acids, C16 and C18-unsaturated, dimerized	Crude dimer

All of the members of this category of substances (hereafter referred to by their common names throughout the test plan) are derived from unsaturated fatty acids, primarily tall oil fatty acids. As with other fatty acid-based products, these substances are complex mixtures and considered to be Class 2 substances.

Crude dimer is manufactured from C18 unsaturated fatty acids through heat treatment with or without an appropriate catalyst. The other members of this category are then obtained from crude dimer either by distillation and/or hydrogenation. (See **Figure 1** on page 8.)

The physical properties of all the members of this group are similar. They are all slightly viscous to viscous liquids and range in color from clear to dark brown. The largest end use for dimer is in the manufacture of polyamide resins for use in adhesives, inks and coatings.

PCA has reviewed existing data on these substances. There are existing data on dimer for many SIDS endpoints. These compounds are non-toxic in acute toxicity tests. Repeat-dose studies show low toxicity and no potential for reproductive effects. Bacterial and mammalian mutagenicity data are negative.

Where applicable, PCA will conduct physical/chemical property and environmental fate testing on all of the substances in the category for which data are not already available. PCA has elected to treat these four substances as a category for purposes of the HPV Program. Therefore, a representative of the category will be tested for the additional required SIDS endpoints. Dimer (CAS # 61788-89-4) has been selected as the representative substance in this category for testing as it has the largest production volume and, in particular the distilled form to be used for testing, has the highest dimer content of the members of this category.

A brief summary of the available data for the substances in this category, and the anticipated additional testing, is presented below in Table 1.

Table 1
Matrix of Available Adequate Data and Proposed Testing On Fatty Acid Dimers and Trimer*

Chemical and CAS #	Required SIDS Endpoints										
	Partition Coef.	**Water Sol.**	**Biodeg.**	**Acute Fish**	**Acute Daph.**	**Acute Algae**	**Acute oral**	**Repeat Dose**	**In vitro genotox (bact.)**	**In vitro genotox (non-bact)**	**Repro/ Develop**
Dimer 61788-89-4	Test	Test	Adeq.	Test	Test	Test	Adeq.	Adeq.	Adeq.	Adeq.	Adeq. Repro/ Test Develop.
Trimer 68937-90-6	Test	Test	Test	C	C	C	C	C	C	C	C
Hydrogenated dimer 68783-41-5	Test	Test	Test	C	C	C	C	C	C	C	C
Crude dimer 71808-39-4	Test	Test	Test	C	C	C	C	C	C	C	C

Adeq. Indicates adequate existing data
Test Indicates proposed testing
C Indicates category read-down from existing or proposed test data on dimer.
* No testing will be conducted for melting point, boiling point, vapor pressure, hydrolysis, photodegradation and transport and distribution between environmental compartments as explained in the test plan.

Physical/Chemical Properties

Physical and chemical properties will be determined for all members of the category when appropriate. However, many of the physical and chemical properties cannot be measured for these substances:

- Melting points will not be determined because these substances are complex mixtures and liquids under ambient conditions and have no specific melting point.
- Boiling points under ambient conditions cannot be determined because these substances are complex mixtures and will decompose before they boil.
- Vapor pressure of these substances under ambient conditions is essentially zero and experimental measurement is inappropriate.
- Water solubility of all of the substances in this category will be determined.

- Partition coefficients of all the substances in this category will be determined. However, the partition coefficient testing likely will yield more than one value representing the various components, rather than a single value representing the mixture.

Environmental Fate

With respect to the SIDS environmental fate endpoints:

- Biodegradation data will be generated for three of the substances in this category. Adequate data are already available for the fourth substance.
- Hydrolysis in water will not be determined for any of the substances in this category because the members of this category contain no hydrolyzable groups.
- Photodegradation is not relevant, since the vapor pressure of these substances is essentially zero and they could not enter the atmosphere.
- Transport and distribution between environmental compartments will not be determined due to the inability to provide usable inputs to the required model.

Ecotoxicity

- Using dimer, acute toxicity to fish, daphnia and algae will be tested under conditions that maximize solubility, but reduce exposure to insoluble fractions, which may cause nonspecific toxicological effects.

Mammalian Toxicity

- For the SIDS human health endpoints, there are adequate data on acute toxicity, repeat dose toxicity, reproductive effects and bacterial and mammalian genotoxicity for dimer.
- Developmental toxicity studies on dimer will be undertaken to fulfill this SIDS endpoint.

The Pine Chemicals Association, Inc. HPV Task Force includes the following companies:

Akzo Nobel Resins
Akzo Nobel - Eka Chemicals Incorporated
Arizona Chemical Company
Asphalt Emulsion Manufacturers Association
Boise Cascade Corporation
Cognis Corporation
Crompton Corporation
Eastman Chemical Co. (including the former Hercules Inc. Resins Division)
Georgia-Pacific Resins Inc.
Hercules Incorporated
ICI Americas (including the former Uniqema)
Inland Paperboard & Packaging, Inc.
International Paper Co. (including the former Champion International Corporation)
Koch Materials Co.
McConnaughay Technologies, Inc.
MeadWestvaco (including the former Mead Corp. and the former Westvaco)
Packaging Corporation of America
Plasmine Technology, Inc.
Raisio Chemicals
Rayonier
Riverwood International
Smurfit – Stone Container Corporation
Weyerhaeuser Co.

The Task Force has filed multiple test plans covering various chemicals. Not all members of the Task Force produce the substances covered by this test plan.

I. Description of Fatty Acid Dimers and Trimer

The Pine Chemicals Association, Inc. (PCA) is sponsoring four HPV chemicals known collectively as Fatty Acid Dimers and Trimer. This category of chemicals consists of:

CAS Number	IUR Name	Common Name
61788-89-4	Fatty acids, C18-unsaturated, dimers	Dimer
68937-90-6	Fatty acids, C18-unsaturated, trimers	Trimer
68783-41-5	Fatty acids, C18-unsaturated, dimers, hydrogenated	Hydrogenated dimer
71808-39-4	Fatty acids, C16 and C18-unsaturated, dimerized	Crude dimer

For convenience, the common names of these substances are used in this test plan.

All the members of this category are produced by the dimerization of C18 unsaturated fatty acids, primarily tall oil fatty acids. As with other fatty acid-based products, these substances are complex mixtures and therefore are considered Class 2 substances.

The classical production process begins by heating unsaturated fatty acid in the presence of an acid-treated clay catalyst to a temperature greater than 200^0 C. Under these conditions, some of the fatty acids dimerize, a lesser amount trimerizes, and some isomerizes to monomer (Zinkel and Russell 1989). This reaction mixture is called crude dimer.

Based on EPA guidance (letter of May 4,1995), the reaction mixture can have two different CAS Registry Numbers depending on its intended use:

- If it is used as the feedstock for the production of dimer, it has CAS # 71808-39-4.

- If it is sold as a commercial raw material for the production of products other than dimer, then it has CAS # 61788-89-4.

The typical fatty acid dimerization process is shown in Figure 1 (see page 8).

Figure 1. Typical Fatty Acid Dimerization Process

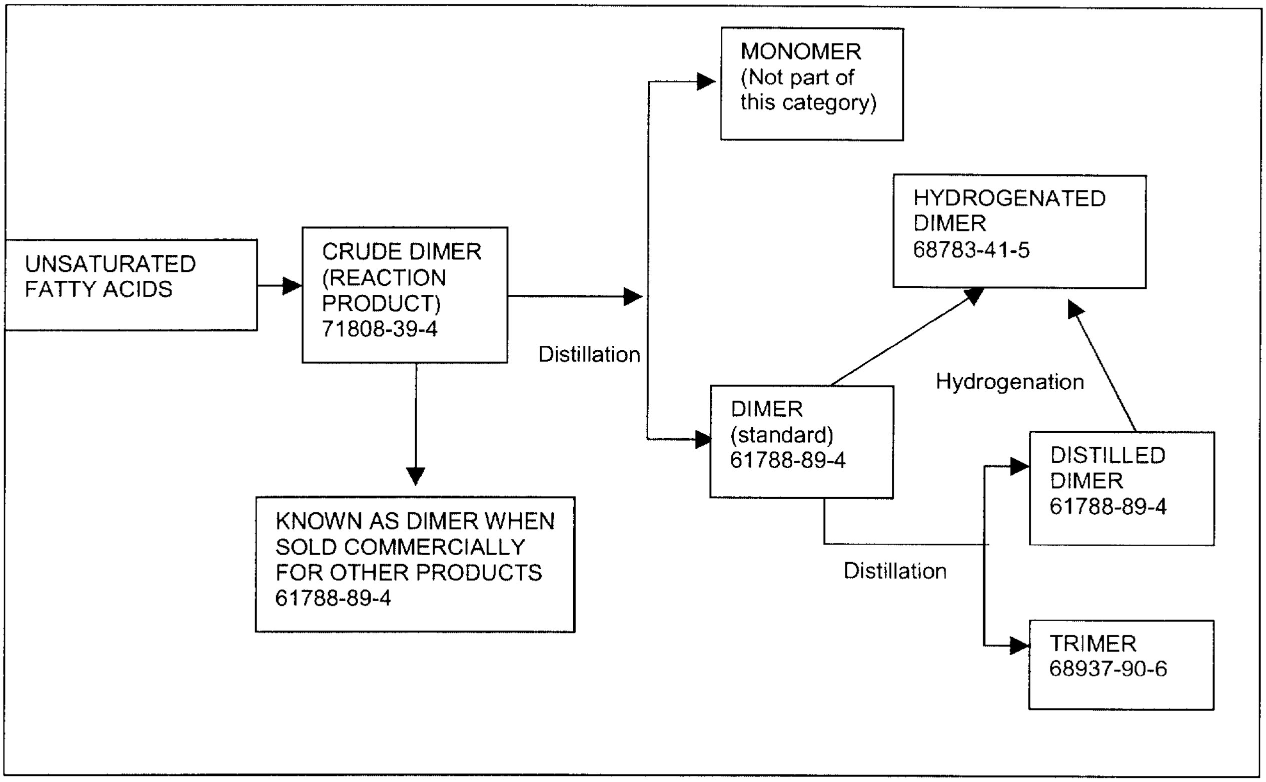


Figure 1 shows schematically how the other members of this category of substances are produced from crude dimer.

- To produce the other members of the category, crude dimer is distilled, which removes most of the monomer, leaving dimer (known in the industry as standard dimer). The monomer acid is not a member of this category, but is included in PCA's Tall Oil Fatty Acid Test Plan.

- Standard dimer can be further distilled to give distilled dimer and trimer.

- Standard dimer and distilled dimer can also be hydrogenated to yield hydrogenated dimer, which has improved stability to heat and oxygen.

Composition

All the members of this category are liquids, ranging in color from clear to dark brown. The viscosity of the members depends on the dimer and trimer content, with crude dimer being a low viscosity liquid and at the other extreme, trimer being a very viscous liquid. The typical composition of the substances in this category is shown in Table 2 (below).

Table 2

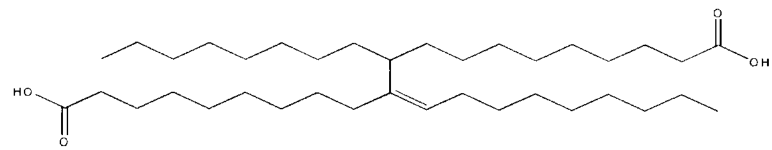
Representative Compositions of Dimer Acids

Substance	**C18 Acids (Monomeric) %**	**C36 Acids (Dimeric) %**	**C54 Acids (Trimeric) %**
Dimer			
Crude dimer	30	60	10
Dimer	2	80	18
Distilled dimer	1	94	5
Trimer	<1	40	60
Hydrogenated dimer	2	80	18

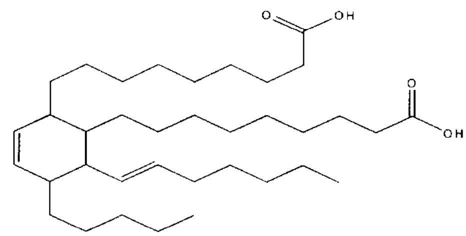
The composition of dimer and trimer is complex. Several representative dimer structures are shown schematically in Figure 2 (see page10). Dimers and trimers are predominantly cyclic addition compounds of unsaturated fatty acids, although bicyclic, non cyclic and other structures are present.

Figure 2. Representative Structures of Fatty Acid Dimers. (Many geometric isomers of the structures below are present in fatty acid dimers.)

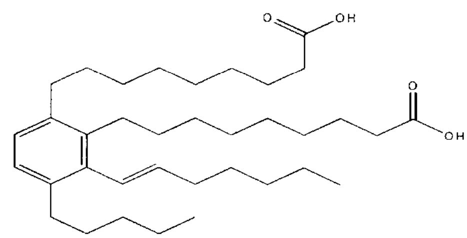
Acyclic Dimer



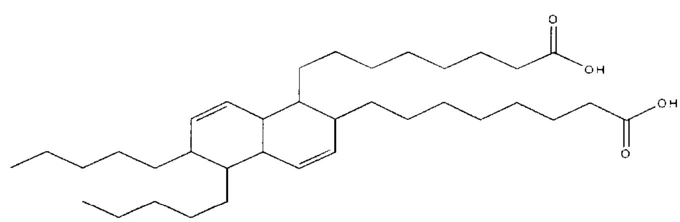
Cyclic Dimer



Aromatic



Polycyclic



A. Commercial Uses of Dimer Acids

Dimer is used primarily in the production of non-nylon polyamide resins. Polyamide resins are used in various formulations for high performance adhesives and printing inks for flexible packaging, and as a cross linking agent for epoxy resins. Dimer is also used as a raw material for the production of surface coatings, primarily coatings for metal coils. Derivatives of dimer (imidazolines) are used as corrosion inhibitors in petroleum production and refining. Trimers find application as a component in oil well drilling fluids.

B. Complexity of Analytical Methodology

All the substances in this category are Class 2 substances. This, combined with the fact that they are essentially insoluble in water and decompose rather than vaporize on heating at ambient pressure, creates a variety of analytical challenges. The large size of the dimer and trimer molecules and their non-volatility makes gas chromatography impractical. The commonly used technique for analyzing members of this category is gel permeation chromatography. However, this technique is not normally used for detecting low levels of dimer; rather, it is used for determining the monomer, dimer and trimer content of dimer products at percentage levels.

Preliminary method validation undertaken as a predicate to PCA's proposed HPV testing has indicated that under the correct conditions it should be possible to use this analytical method to determine levels of dimer as low as, or even <10 ppm, the expected solubility of these substances in water. While the level of dimer to be detected will be considerably higher in animal feeding studies, the analysis will be complicated by the presence of materials in the animal feed that are similar to dimer with respect to molecular weight and solubility. However, it is anticipated that this complication can be overcome and the selected technique will be satisfactory for the planned studies.

II. Rationale for Selection of Representative Compound for Testing

Dimer (CAS # 61788-89-4) has been selected as the representative substance in this category for testing for the applicable SIDS ecotoxicity and developmental toxicity tests, as shown in Table 3 (identical to Table 1). Chemically, the members of this category are very similar as they are all essentially mixtures of monomer, dimer and trimer. Dimer has been selected as the representative test substance for ecotoxicity and developmental toxicity testing for several reasons. It is the most commercially important substance, with the largest production volume. Dimer, and in particular the distilled form to be used for testing, has the highest dimer content of any of the members of this category so that the results will be most representative of the category.

Since all of the substances in this category are either dimers or trimers of fatty acids, they are in the same family of compounds. Thus, these substances meet EPA's criterion of using the "family approach" to group chemicals into a category to examine related chemicals. In summary, these four substances -- all from the same family -- fit the requirements of the EPA's HPV Challenge Program for a category, and dimer is the most appropriate representative test material from this category.

III. Review of Existing Data and Development of Test Plan

PCA has undertaken a comprehensive evaluation of all relevant data on the SIDS endpoints of concern for the substances in this category. Considerable data on dimer (CAS # 61788-89-4) are available that satisfy many of the SIDS endpoints for this category.

The availability of the data on the specific SIDS endpoints is summarized in Table 3 (identical to Table 1). Table 3 also shows data gaps that will be filled by additional testing and areas where data from dimer will be generalized to other category members.

Table 3
Matrix of Available Adequate Data and Proposed Testing On Fatty Acid Dimers and Trimers*

Chemical and CAS #	Required SIDS Endpoints										
	Partition Coef.	**Water Sol.**	**Biodeg.**	**Acute Fish**	**Acute Daph.**	**Acute Algae**	**Acute oral**	**Repeat Dose**	**In vitro genotox (bact.)**	**In vitro genotox (non-bact)**	**Repro/ Develop**
Dimer 61788-89-4	Test	Test	Adeq.	Test	Test	Test	Adeq.	Adeq.	Adeq.	Adeq.	Adeq. Repro/ Test Develop.
Trimer 68937-90-6	Test	Test	Test	C	C	C	C	C	C	C	C
Hydrogenated dimer 68783-41-5	Test	Test	Test	C	C	C	C	C	C	C	C
Crude dimer 71808-39-4	Test	Test	Test	C	C	C	C	C	C	C	C

Adeq. Indicates adequate existing data
Test Indicates proposed testing
C Indicates category read-down from existing or proposed test data on dimer.
* No testing will be conducted for melting point, boiling point, vapor pressure, hydrolysis, photodegradation and transport and distribution between environmental compartments as explained in the test plan.

A. Evaluation of Existing Physicochemical Data and Proposed Testing

The basic physicochemical data required in the SIDS battery includes melting point, boiling point, vapor pressure, partition coefficient (K_{ow}), and water solubility.

Such data are often meaningless for Class 2 substances such as those that comprise the dimer acid category. These substances are composed of a complex mixture of substances and are often difficult to characterize. The members of this category are not only Class 2 substances, but are derived from natural sources. Their composition is variable and cannot be represented by a single chemical structural diagram. Due to this "complex mixture" characteristic of dimer, some physical property measurements, such as partition coefficient do not give single definitive results because the methodology used to determine these properties will actually fractionate or partition the substance into various components. Since the methodology will alter the actual sample composition, the results are likely to be erroneous, difficult to interpret, or meaningless.

1. Melting Point

Melting points will not be determined because all of the substances in this category are liquids under ambient conditions.

2. Boiling Point

All of the substances in this category are produced at high temperatures, and generally by high vacuum distillation, and are non-volatile liquids at ambient temperatures. A boiling point at ambient temperature has no significance because these materials will thermally decompose before they boil. Accordingly, measurement of this property is inappropriate for all the substances in this category.

3. Vapor Pressure

Vapor pressures for the substances in this category are effectively zero at ambient temperatures, and their experimental measurement is inappropriate.

4. Water Solubility

Assuming adequate analytical sensitivity can be achieved, the water solubility of all of the substances in this category using OECD (105) will be determined.

5. Partition Coefficient

The partition coefficient (i.e., K_{ow}) for all of the substances in this category will be determined using OECD method 107. It is likely that more than one K_{ow} value, rather than a single value, will be generated when this endpoint is determined. This outcome reflects the complex nature of Class 2 mixtures.

Summary of Physicochemical Properties Testing: The water solubility (OECD method 105) and partition coefficients (OECD method 107) of all of the substances in this category will be determined. Tests for melting point, boiling point, and vapor pressure are inapplicable to these substances.

B. Evaluation of Existing Environmental Fate Data and Proposed Testing

The fate or behavior of a chemical in the environment is determined by the reaction rates for the most important transformation (degradation) processes. The basic environmental fate data covered by the HPV Program include biodegradation, stability in water (hydrolysis as a function of pH), photodegradation and transport and distribution between environmental compartments.

1. Biodegradation

Biodegradability provides a measure for the potential of compounds to be degraded by microorganisms. Depending on the nature of the test material, several standard test methods are available to assess potential biodegradability.

One of the chemicals in this category (dimer) has existing data on the biodegradation endpoint. Biodegradation for the other three substances will be determined using OECD protocol 301B.

2. Hydrolysis

Hydrolysis as a function of pH is used to assess the stability of a substance in water. Hydrolysis is a reaction in which a water molecule (or hydroxide ion) substitutes for another atom or group of atoms present in an organic molecule. None of the substances in this category contain a functional group that would be susceptible to hydrolysis. Therefore, hydrolysis need not be measured.

In addition, low water solubility often limits the ability to determine hydrolysis as a function of pH. All of the substances in this category have very low solubility in water. Therefore, these materials are expected to be stable in water and it would be unnecessary to attempt to measure the products of hydrolysis.

3. Photodegradation

Due to their lack of any vapor pressure under ambient conditions, there is essentially no opportunity for any of the fatty acid dimers or trimer to enter the atmosphere. Thus, photodegradation is irrelevant. In addition, based on the constituents in these complex mixtures, there is no reason to suspect that they would be subject to breakdown by a photodegradative mechanism. Consequently, this endpoint will not be determined for any of the substances in this category.

4. Transport and Distribution between Environmental Compartments

The transport and distribution between environmental compartments is intended to determine the ability of a chemical to move or partition in the environment. The determination of this property requires the use of various models (e.g., level

III model from the Canadian Environment Modeling Centre at Trent University). For Class 2 substances such as dimer and related compounds, the required inputs to the model are either not available or not feasible to determine including molecular mass, reaction half-life estimates for air, water, soil, sediment, aerosols, suspended sediment, and aquatic biota. In addition, while the partition coefficient is also required and can be determined, the multiple K_{ow} values typically derived for these substances are a consequence of sample fractionation and reflect various components in the mixture and are not representative of the mixture itself. Consequently, due to the inability to provide usable inputs to the required model, no determination of transportation and distribution between environmental compartments will be undertaken for any of the substances in this category.

Summary of Environmental Fate Testing: Biodegradation data will be generated (using OECD 301B) for three of the compounds in this category; there are existing biodegradation data for dimer. Photodegradation, hydrolysis and transport and distribution between environmental compartments are not applicable to these substances.

C. Evaluation of Existing Ecotoxicity Data and Proposed Testing

The basic ecotoxicity data that are part of the HPV Program include acute toxicity to fish, daphnia and algae. Dimer will be tested for these endpoints under conditions that maximize the solubility under the specific test exposure conditions, but reduce exposure to insoluble fractions, which may cause nonspecific toxicological effects. In addition, the effect of both filtering, to further minimize nonspecific physical effects, and of reducing the pH to the lower end of the acceptable range for test organism survival, will also be investigated for changes in toxicological effects. The results of preliminary tests will be used to select the most appropriate test conditions for the definitive test for each species.

Summary of Ecotoxicity Testing: The acute toxicity of distilled dimer to fish (OECD 203), daphnia (OECD 202) and algae (OECD 201) will be tested under conditions that maximize solubility, but reduce exposure to insoluble fractions, which may cause nonspecific toxicological effects.

D. Evaluation of Existing Human Health Effects Data and Proposed Testing

1. Acute Oral Toxicity

Acute oral toxicity studies investigate the effect(s) of a single exposure to a relatively high dose of a substance. This test is conducted by administering the test material to animals (typically rats or mice) in a single gavage dose. Harmonized EPA testing guidelines (August 1998) set the limit dose for acute oral toxicity studies at 2000 mg/kg body weight. If less than 50 percent mortality is observed at the limit dose, no further testing is needed. A test substance that shows no effects at the limit dose is considered essentially nontoxic. If compound-related mortality is observed, then further testing may be necessary.

Summary of Available Acute Oral Toxicity Data

Dimer is non-toxic following acute oral exposure, with LD_{50} values > 2,000 mg/kg in several studies. Hydrogenated dimer is also non-toxic following acute oral exposure with an LD_{50} value > 5,000 mg/kg.

Summary of Acute Oral Toxicity Testing: The representative compound in this category (dimer) has been tested for acute oral toxicity and found to be non-toxic (i.e., LD_{50} > 2000 mg/kg). In addition, hydrogenated dimer is also non-toxic with an LD_{50} value > 5,000 mg/kg.

2. Repeat Dose Toxicity

Subchronic repeat dose toxicity studies are designed to evaluate the effect of repeated exposure to a chemical over a significant period of the life span of an animal. Typically, the exposure regimen in a subchronic study involves daily exposure (at least 5 consecutive days per week) for a period of not less than 28 days or up to 90 days (i.e., 4 to 13 weeks). The HPV program calls for a repeat dose test of at least 28 days. The dose levels evaluated are lower than the relatively high doses used in acute toxicity (i.e., LD_{50}) studies. In general, repeat dose studies are designed to assess systemic toxicity, but the study protocol can be modified to incorporate evaluation of potential adverse reproductive and/or developmental effects.

Summary of Available Repeat Dose Toxicity Data

There are existing data that demonstrate low toxicity for dimer. This substance was administered to Sprague-Dawley rats at dietary concentrations of 0, 0.1, 1, or 5% for 13 weeks. The approximate doses were 0, 100, 1,000, or 5,000 mg/kg/day. Parameters evaluated included clinical signs, body weight, food and water consumption, hematology, clinical chemistry, and gross pathology, organ weights and microscopic pathology.

No deaths occurred and no treatment-related effects on clinical signs, body weight, body weight gain, or water intake were noted. A transient, statistically significantly decrease in food consumption occurred in the 5% males and females during the first four weeks of study. Slight changes in hemoglobin (increased in 5% males) and prothrombin time (increased in 1% females and 5% males and females) were considered not to be toxicologically significant. Treatment-related clinical chemistry changes included increased alkaline phosphatase (1 and 5% males and females) and ALT (5% males and females), and decreases in total cholesterol and triglycerides (1 and 5% males and females), total serum protein and albumin (5% males and females), and betaglobulin fraction (1 and 5% males). While some decreased organ weights were noted, they did not correlate to any microscopic changes. Although a no-effect-level was not identified in this study, 0.1% (approximately 100 mg/kg/day) can be considered a no-observed-adverse-effect-level (NOAEL) based on minimal increases in clinical chemistry parameters and histopathological findings at the higher doses.

Summary of Repeat Dose Toxicity Testing: Dimer has been tested for repeat dose toxicity in a 13 week study. In this study, the NOAEL was approximately 100 mg/kg/day, indicating that this compound has low toxicity.

3. Genotoxicity – In vitro

Genetic testing is conducted to determine the effects of substances on genetic material (i.e., DNA and chromosomes). The gene, which is composed of DNA, is the simplest functional genetic unit. Mutations of genes can occur spontaneously or as a consequence of exposure to chemicals or radiation. Genetic mutations are commonly measured in bacterial and mammalian cells, and the HPV program calls for completing both types of tests.

Summary of Available Genotoxicity Data

Dimer has been tested for potential genotoxicity in several test systems including the Ames *Salmonella* assay, mouse lymphoma cell assay and a metaphase chromosome analysis of human lymphocytes. None of these test systems showed any indication of genotoxicity.

Summary of Genotoxicity Testing: Because dimer has been tested and found negative in three genotoxicity assays, no additional testing for this endpoint will be undertaken.

4. Reproductive and Developmental Toxicity

Reproductive toxicity includes any adverse effect on fertility and reproduction, including effects on gonadal function, mating behavior, conception, and parturition. Developmental toxicity is any adverse effect induced during the period of fetal development, including structural abnormalities, altered growth and post-partum development of the offspring.

The "toxicity to reproduction" aspect of the HPV Challenge Program can be met by conducting a reproductive/developmental toxicity screening test or adding a reproductive/developmental toxicity screening test to the repeat dose study (OECD 421 or OECD 422, respectively).

Summary of Reproductive/Developmental Toxicity Data

As noted in the SIDS guidelines for the reproduction toxicity endpoint, *"when a 90-day repeated dose study is available and demonstrates no effects on the reproductive organs, in particular the testes, then a developmental study can be considered as an adequate test to complete information on reproduction/developmental effect."* Dimer has been tested in a 13-week repeat dose study. This study included histopathology of reproductive organs (*i.e.*, testes, ovaries, uterus) and showed no evidence of reproductive organ toxicity at any dose level. Therefore, this study satisfies the SIDS reproductive toxicity endpoint.

Summary of Reproductive/Developmental Testing: Dimer did not demonstrate any effects on reproductive toxicity in a repeat dose study. However, since this study did not evaluate potential developmental toxicity, dimer will be tested for this endpoint with OECD method 421.

References

Zinkel, D.F. and Russell, J., Eds. 1989. Naval Stores. Production, Chemistry, Utilization. Pulp Chemicals Association, New York.

March 2002